GPBAR1/TGR5 mediates bile acid-induced cytokine expression in murine Kupffer cells.

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Public Summary:
GPBAR1/TGR5 is a novel plasma membrane-bound G protein-coupled bile acid (BA) receptor. BAs are known to induce the expression of inflammatory cytokines in the liver with unknown mechanism. Here we show that without other external stimuli, TGR5 activation alone induced the expression of interleukin 1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) in murine macrophage cell line RAW264.7 or murine Kupffer cells. The TGR5-mediated increase of pro-inflammatory cytokine expression was suppressed by JNK inhibition. Moreover, the induced pro-inflammatory cytokine expression in mouse liver by 1% cholic acid (CA) diet was blunted in JNK-/- mice. TGR5 activation by its ligands enhanced the phosphorylation levels, DNA-binding and trans-activities of c-Jun and ATF2 transcription factors. Finally, the induced pro-inflammatory cytokine expression in Kupffer cells by TGR5 activation correlated with the suppression of Cholesterol 7alpha-hydroxylase (Cyp7a1) expression in murine hepatocytes. These results suggest that TGR5 mediates the BA-induced pro-inflammatory cytokine production in murine Kupffer cells through JNK-dependent pathway. This novel role of TGR5 may correlate to the suppression of Cyp7a1 expression in hepatocytes and contribute to the delicate BA feedback regulation.

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